Medical Staff Conference

Current Concepts in the Treatment of Tuberculosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD:* *Tuberculosis remains an active and important health problem for Americans. The influx of immigrants from Southeast Asia and Central and South America has focused attention on the high endemic rates of tuberculosis in these populations and the problem of resistance to first-line antituberculous therapy. This timely review provides a rationale and guidelines for "short-course" therapy for tuberculosis that keeps these concerns in mind.*

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IRA B. TAGER, MD, MPH:† In this review I intend to summarize a conceptual framework of how major antituberculous drugs are used in modern, short-course chemotherapy and to provide a classification of the behavior of these drugs that will be useful, in a generic way, for designing therapeutic regimens for tuberculosis. I will also describe some selected applications of recent knowledge to the design of chemotherapeutic regimens.

Before presenting specific aspects of antituberculous therapy, a few general comments about the tubercle bacillus are necessary. The tubercle bacillus is an obligate aerobic bacterium that is capable of growing both intracellularly and extracellularly. The organism has a very long average replication time, approximately 20 hours, when studied in vitro.[1] In biologically relevant situations, in both animal and human tuberculosis, a very wide range of replication times, from rapid to dormant states, can be observed. This characteristic of the tubercle bacillus is important in the understanding of how chemotherapeutic regimens are designed.

Drug resistance occurs in virtually all populations of tubercle bacilli that have not been exposed to antituberculous drugs.[1,2] The appearance of such natural resistance is largely a statistical phenomenon based on the population density of the organism, the probabilities of which differ somewhat for the different drugs (Table 1). This fact was recognized very early,[3] and prevention of the emergence of drug-resistant organisms is one of the reasons why antituberculous chemotherapy, almost from its inception, has been based on the use of more than one drug.

Finally, by way of introduction, several terms require definition. Evaluation of the bactericidal activity of antituberculous drugs in vivo, in contrast to in vitro assessment, refers to the degree of killing of organisms as assessed over the first two days of therapy in an animal model or in disease in humans. The bactericidal activity of the drugs is distinguished from another characteristic called the "sterilizing activity" of the drug, which is defined as the ability of the drug to kill all tubercle bacilli as rapidly as possible. It is this latter characteristic of the drugs that is responsible for the ultimate cure of the disease, as will be discussed. In experimental and in clinical situations, the sterilizing capacity of antituberculous drugs is assessed by the evaluation of the rate of conversion to sputum negativity at two months of therapy and by relapse rates that follow the conclusion of therapy, generally, in the case of humans, over the first three years after therapy has been completed.

Figure 1[4] presents a simplified working model of how antituberculous drugs work in complex biologic systems. This model defines the idealized tuberculous lesion as having three components—not necessarily physically separated from each other, but constituting a complex lesion. One component is the cavitary lesion, characterized by large bacterial populations, generally in the range of 10^7 to 10^9 organisms[4]; this lesion, therefore, represents the population out of which naturally occurring drug resistance is most likely to emerge. Organisms in this population tend to be actively growing. The pH environment tends to be neutral or alkaline (the importance of which will become evident during the discussion of the behavior of the drugs). A second element of the model is the closed caseous lesion, which is believed to have a population in the range of 10^4 to 10^5 organisms.[3] Metabolically, these organisms are slowly or only intermittently growing and, in some cases, may be dormant. In the initial conceptualization of this model, which will be presented in modified form subsequently, it was thought that the caseous component represented a uniformly neutral pH environment. The final part of the ideal lesion is the intracellular component, the pulmonary macrophage population, made up of about 10^4 to 10^5 slowly replicating organisms. This component is thought to be in an acid environment for reasons that will be presented below.

In the context of the model, failure of therapy relates to two different problems (Figure 2).[1] One problem is failure due to the selection of drug-resistant organisms that occur naturally in the environment and are found in a very discrete, large population of rapidly growing organisms. The second and most common cause of failure is due to the persistence of

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TABLE 1.—*Frequency of Resistant Tubercle Bacilli in Populations of Bacteria Unexposed to Antituberculous Drugs*

Drug	Frequency
Isoniazid	$1.5 \text{ to } 3.5 \times 10^{-6}$
Streptomycin sulfate	$0.5 \text{ to } 4.0 \times 10^{-6}$
Rifampin	$1.0 \text{ to } 3.0 \times 10^{-8}$
Ethambutol hydrochloride	$0.5 \text{ to } 1.0 \times 10^{-4}$

organisms. These "persistors" are metabolically relatively inactive or dormant, and they reside in two separate but somewhat overlapping populations. The design of antituberculous regimens has been predicated on the need to deal with these two sets of population dynamics and their implications for the success or failure of therapy.

Before going on to a discussion of the individual drugs, some of the data that have been used to formulate the metabolic and environmental characteristics of the model in Figure 1 will be reviewed. Quantitative estimates of the bacterial populations in cavitary and caseous lesions have been derived from direct measurements of surgically removed lung tissue.[3] The estimate for the intracellular population is probably the least accurate of the three, but is reasonable, based on early studies on the behavior of pyrazinamide in murine tuberculosis.[5]

Direct measurements of cavitary and caseous lesions have shown that their average pH is about 7 with a range of 6.8 to 7.2.[6] Recent work, to be discussed later, suggests that the caseous lesion is likely, in fact, to be a complex set of microenvironments with small, localized areas of inflammation and relatively low pH. Because the activity of pyrazinamide, a very important drug in modern therapeutic regimens, and the aminoglycosides (such as streptomycin) is pH-dependent,[8] inferences about the pH environments of the model in Figure 1 are of considerable importance. The inference that the bacterial populations in macrophages might be in an acid environment is derived from the knowledge of the way in which pyrazinamide acts. It has little antituberculous activity in vitro at a pH above 5.6,[7,8] but does kill tubercle bacilli within macrophages in in vitro experiments in which the extracellular environment is maintained at pH 7.[9]

Isoniazid and rifampin are two of the mainstays of current therapy, and they illustrate some of the complexities in understanding how antituberculous drugs behave. Both isoniazid and rifampin in vitro have equivalent antituberculous activity[10,11] and they are both active over a broad range of pHs.[10] In vivo, however, isoniazid appears to have a greater early bactericidal activity than rifampin. In patients treated with a single drug as part of their initial therapy,[12] the use of isoniazid leads to about three fourths of a log per day reduction in bacterial counts over the first two days of therapy, whereas that of rifampin results in a reduction somewhat less than a third of that for isoniazid over the first 48 hours of therapy. The effect of adding rifampin to a regimen of other drugs over the first two days is very limited relative to the effect of adding isoniazid. Moreover, additional data from in vitro studies indicate that isoniazid and rifampin actually appear to be antagonistic during the first two days of therapy.[10]

The above findings are completely at odds with the very important role that rifampin has come to have in the therapy for tuberculosis. The explanation for this apparent paradox lies in the fact that isoniazid and rifampin differ fundamentally in the way in which they act on slowly or intermittently replicating organisms, both in vitro and in vivo. Figure 3 illustrates the differences in vitro.[13] Tubercle bacilli were grown in cultures kept regularly at 8°C and intermittently (one to six hours a day) at 37°C. By 15 days, those cultures exposed to rifampin achieved a level of killing of these intermittently growing organisms that was just about achieved at about one month of exposure to isoniazid. Thus, rifampin in vitro is much more rapid in the onset of its activity against these relatively inactive organisms that are thought to be the cause of most of the long-term failures of chemotherapy. This differential effect has been substantiated in vivo also. When mice treated with a regimen of isoniazid and streptomycin sulfate and a one-month course of rifampin are compared with mice treated with a regimen of isoniazid and streptomycin alone,[10] there is an approximate threefold greater reduction in the number of bacteria in the rifampin-treated group after a month of therapy. More important, at four months, three months after the rifampin therapy has been stopped, there is about a 45-fold reduction in the number of persisting organisms in the rifampin-treated mice. This observation supports the fact that rifampin is acting very rapidly on a relatively slow-growing population of organisms that isoniazid therapy alone is not capable of eradicating despite three months of additional therapy. Moreover, 75% of animals given a regimen of isoniazid and streptomycin for tuberculosis for 18 months show lung cultures positive for *Mycobacterium tuber-*

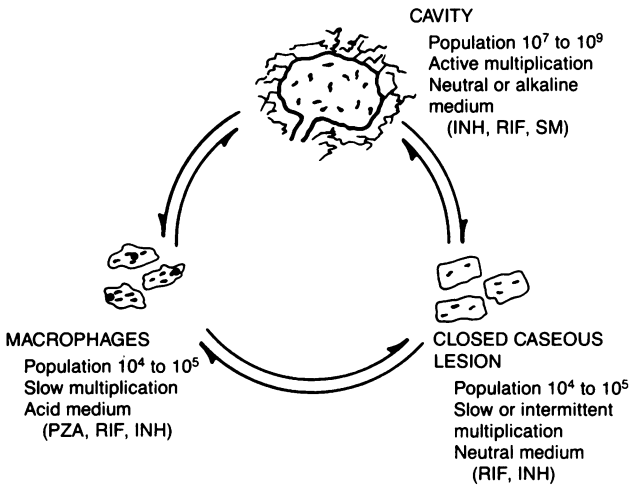

Figure 1.—Populations of *Mycobacterium tuberculosis* in a tuberculous host. Drugs in parentheses refer to agents effective against the specific population (from Dutt and Stead,[3] by permission). INH = isoniazid, PZA = pyrazinamide, RIF = rifampin, SM = streptomycin sulfate

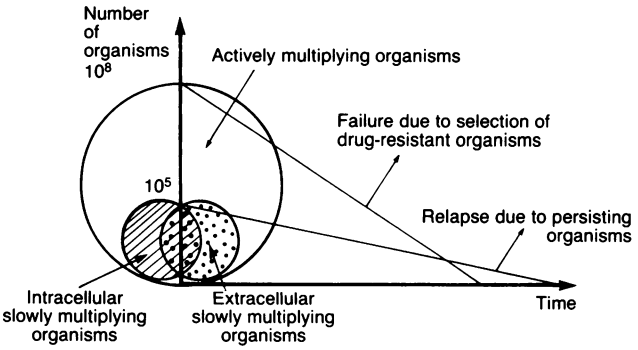

Figure 2.—Results of therapy for tuberculosis in relation to the population dynamics of the tubercle bacilli (from Grosset,[1] by permission).

culosis three to six months after the cessation of therapy versus 0% for animals treated with a nine-month regimen of isoniazid and rifampin.[1]

Pyrazinamide, as indicated above, is active only in an acid environment,[8] but, like rifampin, it has the unique capacity to rapidly sterilize tuberculous lesions in biologic systems.[5,10] In mice treated with a regimen of isoniazid and streptomycin,[14] 70% of the animals still have positive cultures of their lungs after 12 months of therapy. In pyrazinamide-treated animals, virtually all the lungs are sterilized by 6 months, and by 12 months essentially all of the animals have negative lung cultures. These data also indicate that most of the drug's effect occurs early in the course of therapy. Similarly, in human tuberculosis, pyrazinamide appears to exert its most dramatic effects during the first two months of therapy because adding it during the first two months of multiple drug regimens reduces considerably the relapse rates after the cessation of therapy; continuing the drug therapy beyond two months confers relatively little additional benefit.[14]

The model presented in Figure 1 indicates that pyrazinamide and rifampin act on different populations of bacteria that are dormant or slowly metabolizing and that they are not simply overlapping drugs. Three lines of evidence have been offered to support this concept.[15] Data on the effects of antituberculous drugs on quantitative sputum cultures during the first 14 days of therapy suggest that these two drugs do not possess high early bactericidal activity (fall in colony counts over days 0 to 2 of therapy)[10,12,15]; therefore, their sterilizing activity cannot be explained on this basis. The second line of evidence is that referred to in the preceding paragraph on the behavior of pyrazinamide. The final source of evidence is derived from studies of short-course (four months) chemotherapy for pulmonary tuberculosis.[15] All regimens consisted of two months of initial therapy with streptomycin, isoniazid, rifampin and pyrazinamide. The two regimens that contained rifampin for the subsequent two months had lower relapse rates (14% and 11%) than did the regimens that did not contain rifampin (28% and 30%). Such a result would be very unlikely if both agents were acting on the same population of organisms.

Recently, Mitchison and Nunn[7,16] have reconsidered the model in Figure 1 to better account for data that relate to the behavior of pyrazinamide. If the drug were acting only in an intracellular environment on a small bacterial population, it should have relatively little effect on the total bacterial count during the first 14 days of therapy because that population is very small (10^4 organisms in a population of 10^9 or more organisms). Pyrazinamide, however, is capable of killing 97% of an initial bacterial load over the first two weeks of therapy when used by itself.[12] Additionally, in patients who harbor tubercle bacilli that are resistant to the use of isoniazid only or isoniazid and streptomycin, adding pyrazinamide does lead to therapeutic success in a moderate number of cases.[16] Finally, experimental data provide some support for the possibility that there may be localized areas of inflammation within the caseous lesions that have a pH in the range that is optimal for the activity of pyrazinamide (less than 5.6).[7]

On the basis of the above, the model in Figure 4 has been developed. At the beginning of therapy, the bulk of the population of tubercle bacilli is growing rapidly in an environment at physiologic pH. At this stage, isoniazid is the most active drug, rifampin and streptomycin participate to a lesser extent and, basically, pyrazinamide is inactive. As the bulk of the bacteria is killed and as the host mounts an inflammatory response to the infection, tubercle bacilli are inhibited by the host response and now also find themselves in a pH environment that is much more conducive to the activity spectrum of pyrazinamide. At this point, pyrazinamide and rifampin are capable of killing these slowly growing organisms rather effectively. There is a continual movement of organisms between these two microenvironments in the early stages of the disease. After several weeks, the inflammation tends to subside and a more chronic fibrotic response is seen. Tubercle bacilli again are largely in areas with little acute inflammation (physiologic pH), growing relatively slowly, and, therefore, rifampin becomes the critical drug in the killing of these organisms. The main reason why antituberculous therapy before the advent of rifampin required 18 months rather than the six to nine months used currently is that isoniazid was the only drug available that was capable, over the long term, of killing these relatively metabolically inactive organisms. Because its effect is relatively slow, it had to be given for a long period of time. The same is probably true of pyrazinamide because its ongoing activity depends on the constant cycling of inflammation-no inflammation.

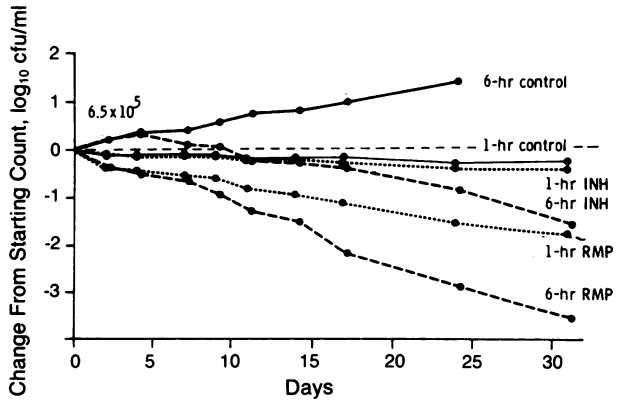

Figure 3.—Bactericidal activity of rifampin (RMP) and isoniazid (INH) on cultures of *Mycobacterium tuberculosis* grown at 8°C and exposed on 5 days each week to 37°C for 1 or 6 hours (from Dickinson and Mitchison,[13] by permission). cfu = colony-forming units

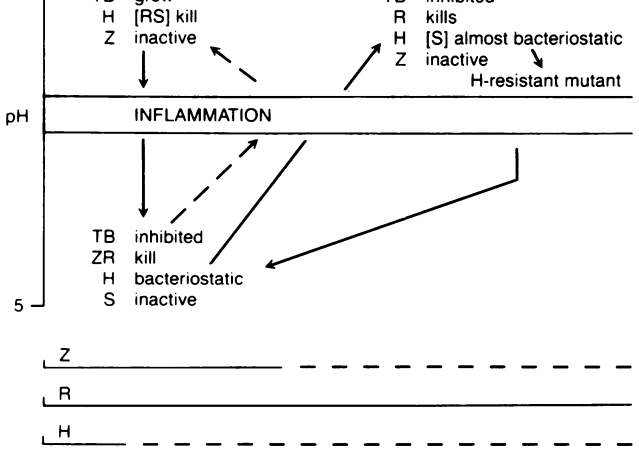

Figure 4.—Role of pH and inflammation in modifying the growth of *Mycobacterium tuberculosis* and the action of isoniazid (H), streptomycin (S), rifampin (R) and pyrazinamide (Z) in killing organisms at the start of chemotherapy, during its first weeks and as a result of the growth of resistant tubercle bacilli (TB). The duration of periods of rapid killing (early bactericidal and sterilizing) by Z, R and H is indicated in the lower part (from Mitchison,[7] by permission).

TABLE 2.—*Grading of Antibacterial Drugs Used in the Therapy for Tuberculosis**

Activity	Sterilizing Activity	Prevention of Drug Resistance: 1st Line Drugs	Prevention of Drug Resistance: Reserve Drugs
High	Rifampin	Isoniazid	...
	Pyrazinamide	Rifampin	...
	Isoniazid	Streptomycin sulfate	Ethionamide
	Streptomycin sulfate†	Ethambutol hydrochloride	Cycloserine
	Ethambutol hydrochloride	...	...
Low	...	Pyrazinamide	Capreomycin sulfate

*Adapted from Mitchison.[7]
†Capreomycin sulfate, viomycin sulfate, kanamycin sulfate.

Ethambutol hydrochloride is a drug that does not appear as a major chemotherapeutic agent in the models that have been presented. In vitro and in vivo, ethambutol has moderate bactericidal activity.[11] In vitro, when ethambutol is added to isoniazid or rifampin, it adds little to their capacity to kill tubercle bacilli.[7] Most important, ethambutol has little sterilizing capacity. In murine tuberculosis, ethambutol provides no additional sterilizing capacity to that observed for rifampin.[17] In humans, ethambutol also fails to contribute meaningfully to the sterilizing capacity of regimens that contain rifampin or pyrazinamide, or both.[18] At the end of two months of therapy (assessment of sterilizing capability), 90% of the pyrazinamide-treated patients versus 76% of the ethambutol-treated patients have negative cultures. Twelve months after the cessation of therapy, the failure rate for the pyrazinamide regimen is 1.4% and for the ethambutol regimen it is 7.5%.

Based on the data presented, regimens to treat tuberculosis must include agents that are bactericidal against both rapidly and slowly dividing bacteria and that can prevent the emergence of drug-resistant bacilli. All drugs currently in use to treat tuberculosis can be classified with regard to these properties. Such a classification is presented in Table 2. The ability of drugs to prevent the emergence of resistance has been assessed from therapeutic results obtained in patients with severe tuberculosis—that is, large bacterial populations—who were given various combinations of single- and multiple-drug therapy.[10,15]

How do the above concepts thus far apply to the real-world problems of therapy for tuberculosis? The first issue to consider in this regard relates to the minimum duration of therapy required to achieve the high cure rates that have come to be expected from modern tuberculosis therapy. A compilation of data from a large number of studies that have evaluated the success of therapy in patients with smear- and culture-positive tuberculosis with a variety of treatment regimens, all of which included isoniazid and rifampin and most of which included pyrazinamide, shows that the minimum duration of therapy appears to be about five months. For routine situations, where rifampin can be used in therapy, nine months appears to be the maximum duration necessary. In this regard, it is important to note that the combination of isoniazid and rifampin is not satisfactory for durations of therapy that are shorter than nine months.[19] The failure rate of therapy when these two drugs are used alone for six months is 7% to 9%.[19]

Given these data, what are the reasonable choices available for the therapy for tuberculosis? If a nine-month period is considered appropriate, then the regimen of isoniazid and rifampin (given daily for a month, twice a week for eight months) developed by Dutt and co-workers[20] seems to be the most acceptable of the available choices in terms of ease of administration and degree of toxicity. When a six-month duration seems preferable, isoniazid and rifampin alone are not sufficient, but a number of therapeutically equivalent alternatives are available (Table 3). Considerations of patient compliance and cost would seem to favor those regimens that use intermittent dosing intervals.

TABLE 3.—*Six-Month Regimens for Treatment of Tuberculosis**

Initial/Continuation	Follow-up, Months	% Relapse
IR	30	8
2SIRP/4IRP†	24	0
2SIRP/4IR	24	2
2SIRP/4I_2R_2‡	18	0
$(SIRP)_3$§	18	1
2SIRP/4I_2R_2‡	24	2
2IRP/4I_2R_2‡	24	4

I=isoniazid, P=pyrazinamide, R=rifampin, S=streptomycin sulfate

*Adapted from Snider and co-workers.[19]
†Number in front of regimen indicates number of months—that is, 2 months initial phase/4 months continuation phase.
‡Continuation phase given twice a week.
§All drugs given 3 times a week for 6 months.

In addition to the ability of intensive drug regimens to reduce the duration of therapy to six months, these regimens offer new options for the initial management of tuberculosis where drug resistance is highly suggested—such as in patients from areas of Southeast Asia—or known to be present on the basis of past sensitivity testing, and for the management of patients for whom active tuberculosis is suggested strongly on clinical grounds but for whom all initial culture results are negative.

Table 4 summarizes current experience with various short-course treatment regimens for the management of patients with tubercle bacilli resistant to isoniazid or streptomycin therapy, or both. Regimens containing four or five drugs, at least one of which is rifampin, result in relapse rates of about 8% for patients with organisms resistant to isoniazid, streptomycin or both versus about 4.2% for patients with drug-sensitive organisms. The lower part of the table provides data that indicate that the differences in the sterilizing capacities of pyrazinamide and ethambutol that have been referred to previously carry over as well to situations that involve drug resistance. These data also point out that omitting rifampin in the continuation phase of therapy results in higher rates of relapse in the management of drug-resistant tuberculosis. When resistance to rifampin is present, the outcomes are not nearly as favorable, and therapy would need to be guided more specifically by the results of sensitivity

testing. Fortunately, resistance to rifampin is still relatively uncommon,[17] and, thus, for practical purposes, any of the rifampin-containing intensive regimens listed in Table 3 could be selected for therapy when drug resistance is suspected, even in the absence of confirmation by formal sensitivity test results.

When there is a strong suggestion clinically that a patient has active tuberculosis, but the diagnosis is not accompanied by positive cultures, the intensive drug regimens offer the prospect of very short durations of therapy that have high probabilities of cure. Three months of therapy with streptomycin, isoniazid, rifampin and pyrazinamide provide a greater than 90% probability of curing a patient who has active pulmonary tuberculosis when initial cultures are negative (Table 5).[21] Although this rate of cure is not as high as that achieved with a full six or nine months of therapy (Table 3), the use of three months of intensive therapy does provide a reasonable alternative to a longer course of therapy when the diagnosis of tuberculosis remains unconfirmed by culture.

TABLE 4.—*Relapse (%) After Short-Course Regimens of at Least 6 Months' Duration**

Regimen	Drug-Sensitive Organisms	Drug-Resistant Organisms
IR, SIR	3.6 to 7.3	12.0 to 14.0
4 or 5 drugs with R	4.2	8.0
2SIRP/$S_2I_2P_2$†‡	5.2	11.0
2SIRE/$S_2I_2E_2$†	16.1	36.0

E=ethambutol hydrochloride, I=isoniazid, P=pyrazinamide, R=rifampin, S=streptomycin sulfate

*Adapted from Mitchison and Nunn.[16]

†2 months initial phase/4 months (or more) continuation phase, with drug regimen in continuation phase given twice a week.

‡Some data derived from regimen given for 8 months.

TABLE 5.—*Results of Therapy for Culture-Negative Pulmonary Tuberculosis**

Regimen	Subjects, Number	Relapse or Disease Months After Therapy 1-12	13-24	>24	Total Relapse
Selective chemotherapy†	173	43	9	5	57
2SIRP‡	161	1	5	4	11
3SIRP‡	161	1	3	3	7
3SI(PA)/$6S_2I_2$‡§	160	0	0.6	1.2	2

I=isoniazid, P=pyrazinamide, (PA)=*para*-aminosalicylic acid, R=rifampin, S=streptomycin sulfate

*Adapted from Hong Kong Chest Service.[21]

†Antituberculosis therapy not started until active tuberculosis confirmed by positive culture, radiographic evidence or clinical deterioration; 72% (71/99) of cases of disease in this group subsequently had positive cultures; 48% (15/31) of failures in other groups subsequently had positive cultures.

‡Number in front of regimen indicates number of months.

§Initial phase of regimen/continuation phase; subscripts refer to times per week. This regimen constituted the standard control treatment regimen for this study.

Such therapy also is a better alternative to simply clinically observing such patients because more than 50% of them can be expected to have clinical progression of disease over a 60-month period (Table 5).[21]

In summary, current concepts that have integrated the knowledge gained from experimental models of tuberculosis and the treatment of human tuberculosis provide physicians with new options for short-term therapy that, for practical purposes, have all but ended the need for routine therapy that extends beyond nine months for virtually all types of clinical tuberculosis.[22]

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